

Capsules for oral administration having a delayed release of
the content of the capsule

5 The present invention relates to gelatine capsules having a delayed release of the content of the capsule for use as an oral administration form for dietary supplement products, dietetic products and medicaments, wherein the delay of the release is effected by a plant extract contained in the cap-
10 sule.

In case of many dietary supplement products, dietetic products and medicaments, it is desirable that the active ingredient is released from the administration form at a certain
15 time after ingestion or in a certain portion of the gastroin-
testinal tract. It is the object of this temporally or lo-
cally controlled release either to protect the user against
unpleasant properties of the active ingredient (e.g. bad
taste, mucosa irritant effect, unpleasant eructation) or to
20 protect the active ingredient against degradation by the ag-
gressive gastric juice or to achieve an improved uptake of
the active ingredients into the body by release in the small
intestine.

25 This delayed release is particularly desirable in those cases, when the active ingredients to be applied are plant extracts which cause an unpleasant taste or exhalation upon eructation in case of too rapid disintegration of the capsule or when substances are contained which may be decomposed in
30 the stomach.

A preferred administration form for said dietary supplement products, dietetic products and medicaments is a capsule which may be filled with liquid, semi-solid or solid sub-

stances. In most cases, the shell of the capsule is made of gelatine. Soft gelatine capsules are particularly suitable because their production, filling and sealing is carried out in one step, the content of the capsule is well-protected
5 against environmental influences such as moisture and oxygen, and because these capsules can be taken very easily.

In general, the release of substances from a capsule in the gastrointestinal tract can be controlled by modifying the
10 content of the capsule or by modifying the shell of the capsule. For example, European patent EP 0 243 930 B1 describes a composition encapsulated in gelatine showing a controlled release, which consists of a solid matrix being formed by a liquid filling consisting of a vegetable gum and the active
15 ingredient by adding cations. This type of method has the disadvantage that specific additional adjuvants have to be added to the filling of the capsule in order to obtain a matrix for controlling the release.

20 Preparations and methods wherein the release is achieved by modifying the shell of the capsules either by adding substances to the material of the shell of the capsules or by applying a functional coating on the finished capsules, are employed far more often. An example for controlling the release by additives to the material of the shell of the capsule is described in European patent EP 0 240 581 B1, wherein physiologically and toxicologically harmless aldehydes having at least four carbon atoms are added to the gelatine decoction and the further processing of the decoction into capsules
25 is carried out according to per se known methods. A disadvantage of this method is that additional substances have to be introduced into the capsule shell, which may have an undesired effect on the properties of the capsules or on the encapsulated ingredients.

A specific embodiment of said gelatine capsules hardened with aldehydes is described in European patent EP 1 091 659 B1, wherein the finished capsules are sprayed with a solution of xylose, ethanol and water under the application of heat, followed by a heat treatment over a specific period. This method is technically very complex and very time-consuming because the solvent used has to be removed virtually completely during the process and ethanol as an inflammable organic solvent can only be used under specific technical conditions.

10

A further possibility to influence the release of the content of the capsule are so-called lacquering or coating methods. Polymers are used for this purpose, which are insoluble in the highly acidic gastric juice and which are in contrast soluble in the approximately neutral intestinal juice (i.e. starting from about pH 5-6). In this method, suitable polymers (e.g. hydroxypropylmethylcellulose phthalate) are dissolved and this solution is applied onto the capsules in a rotating tank or in a coater. Simultaneously, the solvent is evaporated by means of large amounts of heated air and the precipitated polymer forms a coating on the capsules. This method is technically very complex and very time-consuming.

Therefore, it is the object underlying the present invention to influence the disintegration of the capsules and the release of the content of the capsules upon oral administration in a new, simplified and safe form.

It has surprisingly been found that this object can be solved by using polyphenol-containing plant extracts as an ingredient of the filling of the capsule, i.e., of the content of the capsule. The term "polyphenols" comprises phenol carboxylic acids, such as gentisinic acid, protochatechuic acid, gallic acid or caffeic acid, as well as flavones such as kaempferol, quercetin, myricetin, isorhamnetin, naringenin,

35

6-prenylnaringenin, 8-prenylnaringenin, isoxanthohumol and glycosides thereof, chalkones such as xanthohumol, isoflavones such as daidzein and genistein, anthocyanins such as pelargonidin, cyanidin, malvidin or delphinidin, tanning agents such as catechin and epicatechin as well as their oligomers and polymers.

Examples of plants that contain larger amounts of polyphenols comprise, but are not limited to the following: Camellia sinensis, Crataegus monogyna, Ginkgo biloba, Humulus lupulus, Hypericum perforatum, Krameria triandra, Potentilla tormentilla, Pterocarpus marsupium, Quercus species, Uncaria gambir, Vaccinium myrtillus, Vitis vinifera.

A common feature of these plants is that they contain a high portion of polyphenols which are capable of interacting with the gelatine of the shell of the capsule. This so-called tanning effect, which has been known per se for a long time, is attributed to the ability of the polyphenols to form bonds with other molecules (in particular with proteins) (described in detail in Hänsel, Sticher, Steinegger, Pharmakognosie - Phytopharmazie, Springer Verlag Heidelberg, 1999, page 877). Gelatine is such a natural protein or polypeptide which is obtained by hydrolytic degradation of collagen.

According to the present invention, polyphenol-containing plant extracts are used for the first time to selectively influence the release of active ingredients from gelatine capsules, wherein this kind of delay of the disintegration can be used for all capsule materials interacting with polyphenols in the way described. A further advantage of these preparations is that the plant extract used is at the same time one of the active ingredients to be applied, i.e. no additional adjuvants such as coating agents, hardening agents

or thickeners have to be added to achieve the delayed release.

Since in most cases plant extracts have a powdery form and
5 cannot be directly filled due to their bad meterability, the
extracts are mixed with lipophilic, liquid carriers which
cannot be mixed with water (such as plant oils) prior to being
filled into capsules. This flowable mixture is well-suited for being filled into capsules. Further substances
10 such as partially or completely hydrogenated plant oils,
beeswax, lecithin, neutral oil, hardened fat and highly dispersed silicon dioxide are optionally added to the filling of
the capsules to adjust the consistency of the mixture and to prevent demixing of the liquid carrier and the solid plant
15 extract. To expedite the dissolving of the content of the capsule which has been released from the capsule, also amphiphilic surfactants and emulsifiers such as sorbitan monoleate can be added.

20 The extracts can be obtained according to production methods known per se in variable composition using solvents such as water, methanol, ethanol, 2-propanol, acetone and the like as well as their mixtures at temperatures in the range of room temperature to 100°C under slight to vigorous mixing or by
25 percolation within 10 minutes to 24 hours under normal pressure or elevated pressure. In order to enrich the active ingredients further concentration steps such as liquid-liquid distribution using, for example 1-butanol/water or ethylacetate/water, adsorption-desorption on ion exchangers, LH20, HP20 and other resins or chromatographic separations on RP18, silica gel and the like can be performed. The further processing to yield dry extracts is carried out according to methods known per se by removing the solvent at elevated temperature and/or reduced pressure.

A particularly preferred embodiment of the capsules having a delayed disintegration is the combination of a polyphenol-containing plant extract and an oil having a high content of omega-3 fatty acids, in particular perilla seed oil, evening primrose seed oil, currant seed oil, fish oil, borage oil or linseed oil, because both the polyphenol-containing plant extracts and said plant oils advantageously influence chronic inflammatory or immunologic diseases as well as fat metabolism disorders.

10

Preferred are gelatine capsules containing one of the following combinations: extracts from *Vitis vinifera* (grape seed extract, i.e., extract from the seeds of red and/or white grapes) and perilla seed oil, extract from *Vitis vinifera* (red wine extract, i.e., extract from red grapes) and perilla seed oil, extract from *Potentilla tormentilla* and linseed oil, extract from *Crataegus monogyna* and linseed oil, extract from *Camellia sinensis* and borage oil, extract from *Ginkgo biloba* and borage oil, extract from *Krameria triandra* and evening primrose seed oil, extract from *Vaccinium myrtillus* and evening primrose seed oil, extract from *Hypericum perforatum* and fish oil, extract from *Humulus lupulus* and fish oil, extract from *Uncaria gambir* and currant seed oil, extract from *Quercus* and currant seed oil, extract from *Pterocarpus marsupium* and perilla seed oil, extract from *Camellia sinensis* and perilla seed oil as well as extract from *Vaccinium myrtillus* and perilla seed oil.

30

According to the present invention, the delay of the release of the active ingredients does not depend on the fact whether the gelatine capsules are hard gelatine capsules or soft gelatine capsules, because these types of gelatine capsules merely differ with respect to their plasticizer content and water content.

35

Example 1:

Perilla seed oil (75 parts) is mixed with hardened fat (12 parts) and heated to 40°C under stirring. Highly dispersed 5 silicon dioxide (5 parts) and grape seed extract (8 parts) are added to the liquid phase and distributed under stirring. 0.6 g each of the suspension obtained is filled into a gelatine capsule. The sealed capsules are stored at elevated temperature.

10

In a disintegration test in artificial gastric juice, the capsules containing the grape seed extract exhibit an extended disintegration time compared to those capsules which do not contain the grape seed extract.

15

Example 2

Perilla seed oil (69 parts) is mixed with hardened fat (11 parts) and heated to 40°C under stirring. Highly dispersed 20 silicon dioxide (5 parts) and red wine extract (15 parts) are added to the liquid phase and distributed under stirring. 0.65 g each of the suspension obtained is filled into a gelatine capsule. The sealed capsules are stored at elevated temperature.

25

In the disintegration test in artificial gastric juice, the capsules containing the red wine extract exhibit an extended disintegration time compared to those capsules which do not contain the red wine extract.

30

Example 3

In the following the results with respect to influencing the disintegration time of soft gelatine capsules by encapsulat-

ing polyphenol-containing plant extracts and storing at various conditions are summarized.

Tables 1 and 2:

5

Increase of the disintegration time of soft gelatine capsules according to example 2 upon storing under various conditions (testing of the disintegration time according to European Pharmacopoeia with respect to 6 capsules in artificial gastric juice, 0.1 N HCl; disintegration time prior to storing = 4 min).

| batch 1 of the capsules | storing conditions | |
|-------------------------|--------------------|-------------|
| storing period [h] | 40°C/75% RH | 40°C/dry |
| 24 | 9 - 11 min | 10 - 13 min |
| 48 | 9 - 11 min | 12 - 14 min |
| 72 | 9 - 12 min | 12 - 14 min |

| batch 2 of the capsules | storing conditions | |
|-------------------------|--------------------|-------------|
| storing period [h] | 40°C/75% RH | 40°C/dry |
| 24 | 8 - 11 min | 11 - 16 min |
| 48 | 9 - 11 min | 12 - 14 min |
| 72 | 9 - 12 min | 12 - 14 min |

15 The initial value for the time to open the capsule prior to incubation at elevated temperature/humidity was 4 minutes. Without the addition of the polyphenol-containing plant extract the disintegration time remains unchanged also upon storage. By adding the plant extract and by storing, the decomposition time of the capsules is extended. Storing in the absence of water vapor results in an increased extension of the disintegration time. Thus, the disintegration time of
20

soft gelatine capsules can be selectively influenced by adding the polyphenol-containing plant extract and by storing under defined conditions as evidenced by two batches of capsules containing two different batches of red wine extract.